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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John C. Salerno		
Application No.:	09/398,405	Group Art Unit:	1642
Filed:	September 16, 1999	Examiner:	S. Ungar
For:	Activators Of Endothelial Nitric Oxide Synthase		

CERTIFICATE OF MAILING

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on 4/19/01 (Date) Christina M. McSweeney (Signature)

Christina M. McSweeney
Typed or printed name of person signing certificate

REPLY TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Restriction Requirement dated December 19, 2000, the claim of Group 32 (Claim 31), drawn to a method of activating endothelial nitric oxide synthase (ENOS), is elected for prosecution with traverse. Applicant reserves the right to file a divisional or continuing application, or take such other appropriate action as deemed necessary to protect the invention(s) of Groups 1-31 and 33-83. Applicants do not hereby abandon or waive any rights in the invention(s) of these other groups. Reconsideration and modification of the restriction requirement is requested.

An extension of time to respond to the Restriction Requirement is respectfully requested. A Petition for an Extension of Time and the appropriate fee are being filed concurrently.

The requirement sets forth 83 different groups for restriction. Because of the complexity of the restriction requirement, the discussion herein of the traversal of the restriction requirement has been limited to particular Groups of interest.

Applicant respectfully requests that certain groups be recombined with elected Group 32. Specifically, Applicant requests that Groups 4, 5-10, 32, 39-44, 56, and 62-67 be combined and examined together. These Groups were selected because of their closely related subject matter. To facilitate discussion, the Groups of interest, the claims encompassed by the Groups, and the subject matter of the Groups are set forth in the following Table.

Group Number	Claims in Group	Subject Matter of Claims in Group
4	16-18	Activators of ENOS which antagonize autoinhibition by a peptide region between about amino acids 590-650 of endothelial nitric oxide synthase (Claim 16); antibody which binds to one or more amino acids between about amino acids 590-650 of ENOS (Claim 17), which activates ENOS (Claim 18)
5-10	16 and 19	Claim 16 (described above); A constitutive NOS activator peptide comprising an amino acid sequences selected from the group consisting of SEQ ID NO:4 (Group 5); SEQ ID NO: 5 (Group 6); SEQ ID NO: 6 (Group 7); SEQ ID NO: 7 (Group 8): SEQ ID NO: 8 (Group 9), and SEQ ID NO: 9 (Group 10), and activating fragments and derivatives (Claim 19)
32	31	A method of activating ENOS, comprising contacting the ENOS with an effective amount of an agent of Claim 16 (described above)
39-44	32	A method of activating ENOS, comprising contacting the ENOS with an effective amount of an agent of Claim 19 (described above)
56	48	A method of treating a disease modulated by production of nitric oxide by ENOS, comprising administering an effective amount of an agent of Claim 16 (described above)
62-67	49	A method of treating a disease modulated by production of nitric oxide by ENOS, comprising administering an effective amount of an agent of Claim 19(described above)

Modification of the restriction requirement to consider these Groups concurrently is appropriate for the reasons set forth below.

The inventions claimed in the subject application arise from the discovery of the existence and identity of regulatory peptides of constitutive nitric oxide synthases ("NOS"), including endothelial and neuronal NOS, that are not found in inducible NOS. This discovery, *inter alia*, gave rise to the ability to selectively inhibit or activate a constitutive NOS (ENOS, NNOS) or inducible NOS (INOS).

Group 32 is drawn to a method of activating endothelial nitric oxide synthase. Applicant's Attorney notes that the Examiner has set forth Groups 32-38 relating to Claim 31, stating that the activator used in the method is an antibody or peptide of SEQ ID NO: 4-9 (Group 32-38, respectively). Claim 31 is drawn to a method of activating endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 16. Claim 16 is drawn to an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase. Claim 16 does not mention SEQ ID NO: 4-9; however, a later claim (Claim 19) does, and Claim 32 refers to Claim 19. It is therefore believed that the features of Claim 19 were mistakenly read into Claim 31, resulting in the separation of Claim 31 into Groups 32-38. It appears, however, that Claim 31 should be embodied in a single Group (e.g., Group 32), because it refers to use of a class of agents (those of Claim 16, i.e., an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase). Thus, there is no apparent subject matter for Groups 33-38 as set forth in the restriction requirement, and for this reason, Applicant has not requested recombination of Groups 33-38 with Group 32. Applicant's Attorney respectfully requests clarification of this aspect of the restriction requirement. It is Applicant's intention by electing Group 32, to elect the group which contains the method of Claim 31 which utilizes the agent of Claim 16: that is, a method of activating endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent, wherein the agent is an activator of endothelial nitric oxide

synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase.

Claim 32, like Claim 31, is drawn to a method of activating endothelial nitric oxide synthase. The method of Claim 32 comprises contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 19. Claim 19 defines activators of constitutive NOS, embodied as the regulatory peptides of the NOS enzymes: it is drawn to a constitutive nitric oxide synthase activator peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:4-9 and activating fragments and derivatives of SEQ ID NO: 4-9. Thus, Claim 32 has been separated into Groups 39-44 (for SEQ ID NO: 4-9, respectively).

Applicant's Attorney requests that Groups 39-44 be recombined with elected Group 32 (as discussed above), as these groups all pertain to methods of activating endothelial nitric oxide synthase (one of the two constitutive nitric oxide synthases), and because each of the activators in Groups 39-44 share a commonality of function with the activator of Group 32 (i.e., activation of a constitutive nitric oxide synthase, endothelial nitric oxide synthase). A single art search will identify relevant art pertaining to activators of endothelial oxide synthase, so recombining these groups would not be unduly burdensome.

Furthermore, Applicant traverses the Examiner's requirement based on the clear statement in MPEP §803.04, and in the Official Gazette Notice dated November 19, 1996, regarding the examination of patent applications containing nucleotide sequences, which state that "...the Commissioner has decided sua sponte to partially waive the requirements of 37 C.F.R. 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. Accordingly, in most cases, up to ten (10) independent and distinct nucleotide sequences will be examined in a single application without restriction." In accordance with these established guidelines, Applicant submits that it is reasonable to examine up to ten nucleotide sequences in the subject application, and that therefore, the six sequences in Groups 39-44 can be recombined.

Claim 48 is drawn to a method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase in a mammal, comprising administering to the mammal an effective amount of an agent of Claim 16. Applicant's Attorney notes that the Examiner has set forth Groups 56-61 relating to Claim 48, stating that the activator used in the method is an antibody or peptide of SEQ ID NO: 4-9 (Group 56-61, respectively). As discussed above, Claim 16 does not mention SEQ ID NO:4-9; rather, it is drawn to an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase. It is believed that the error described above in relation to Claim 31 (where the features of Claim 19 were mistakenly read into Claim 31, resulting in the separation of Claim 31 into Groups 32-38), has been repeated in relation to Claim 48. It appears, therefore, that Claim 48 should be embodied in a single Group (e.g., Group 56), because it refers to use of one class of agents (those of Claim 16, i.e., an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase). Thus, there is no apparent subject matter for Groups 57-61 as set forth in the restriction requirement, and for this reason, Applicant has not requested recombination of Groups 57-61 with Group 32. Applicant's Attorney respectfully requests clarification of this aspect of the restriction requirement. It is Applicant's intention in discussing Group 56, to refer to a group which contains the method of Claim 48 which utilizes the agent of Claim 16: that is, a method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase, comprising administering an effective amount of an agent, wherein the agent is an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase.

Applicant's Attorney requests that Group 56, as described above, be recombined with Group 32, as described above. The methods of Group 32 and Group 56 both utilize the agent of Claim 16: that is, an agent that is an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase. A single art

search will identify relevant art pertaining to such an activator of endothelial oxide synthase, so recombining these two groups would not be unduly burdensome.

Claim 49, like Claim 48, is drawn to a method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase in a mammal. The method of Claim 49 comprises contacting the endothelial nitric oxide synthase with an effective amount of an agent of Claim 19. As indicated above, Claim 19 is drawn to a constitutive nitric oxide synthase activator peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:4-9 and activating fragments and derivatives of SEQ ID NO: 4-9. Thus, Claim 49 has been separated into Groups 62-67 (for SEQ ID NO: 4-9, respectively), in a manner similar to the separation of Claim 32 into Groups 39-44, as discussed above.

Applicant's Attorney notes that Claim 50 has been included with Claim 49 in Groups 62-67, and that the Office Action states that the elected inventions will be examined as drawn to treatment by activation of endothelial nitric oxide synthase. However, Claim 50 is drawn to a method of treating a disease modulated by production of nitric oxide by *neuronal* nitric oxide synthase in a mammal, by administering an effective amount of an agent of Claim 20 (i.e., an activator of *neuronal* nitric oxide synthase which antagonizes autoinhibition by a peptide region of *neuronal* nitric oxide synthase, wherein the region is between about amino acids 820-880 of *neuronal* nitric oxide synthase). Applicant's Attorney respectfully requests clarification of this aspect of the restriction requirement. It is Applicant's intention in discussing Group 62-67, to refer to a group which contains the method of Claim 49 which utilizes the agent of Claim 19: that is, a method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase, comprising administering an effective amount of an agent, wherein the agent is an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase.

Applicant's Attorney requests that Groups 62-67, as discussed above, be recombined with elected Group 32, as discussed above, as well as with Groups 39-44 and 56 as discussed above, as these groups all pertain to methods which utilize activation of endothelial nitric oxide synthase

(one of the two constitutive nitric oxide synthases), and because each of the activators in Groups 62-67 (which are the same as the activators in Groups 39-44) share a commonality of function with the activator in Groups 32 and 56 (i.e., activation of a constitutive nitric oxide synthase, endothelial nitric oxide synthase). A single art search will identify relevant art pertaining to activators of endothelial oxide synthase, so recombining these groups would not be unduly burdensome.

Furthermore, as discussed above, Applicant traverses the Examiner's requirement based on the clear statements in MPEP §803.04, and in the Official Gazette Notice dated November 19, 1996, which allow up to ten independent and distinct nucleotide sequences to be examined in a single application without restriction. In accordance with these established guidelines, Applicant submits that it is reasonable to examine up to ten nucleotide sequences in the subject application, and that therefore, the six sequences in Groups 62-67 (and also in Groups 39-44) can be recombined.

As discussed above, Claim 16 (falling in Group 4) is drawn to an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase. Because this activator is the activator used in the methods described in Claim 31 (Group 32) and Claim 48 (Group 56), Applicant's Attorney requests that Group 4 be recombined with elected Group 32 (as discussed above), and also with Group 56 (as discussed above), as these groups have as a common feature the activator of Claim 16 (i.e., an activator of a constitutive nitric oxide synthase, endothelial nitric oxide synthase). A single art search will identify relevant art pertaining to activators of endothelial oxide synthase, so recombining these groups would not be unduly burdensome.

As also discussed above, Claim 19 is drawn to a constitutive nitric oxide synthase activator peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:4-9 and activating fragments and derivatives of SEQ ID NO: 4-9. Thus, Claim 19 has been separated into Groups 5-10 (for SEQ ID NO: 4-9, respectively). Because this activator is the activator used in the methods described in Claim 32 (Groups 39-44) and Claim 49 (Groups

62-67), Applicant's Attorney requests that Groups 5-10 be recombined with Groups 39-44 and 62-67. Furthermore, Applicant's Attorney requests that they be recombined with elected Group 32, and also with Group 56 and Group 4, as these groups have as a common feature an activator of endothelial nitric oxide synthase. A single art search will identify relevant art pertaining to activators of endothelial oxide synthase, so recombining these groups would not be unduly burdensome.

In summary, Group 32 has been elected as described above (encompassing the method of Claim 31 which utilizes the agent of Claim 16: that is, a method of activating endothelial nitric oxide synthase, comprising contacting the endothelial nitric oxide synthase with an effective amount of an agent, wherein the agent is an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase). It is requested that Group 56 (Claim 48) be recombined with Group 32, because it similarly utilizes the agent of Claim 16: that is, it is drawn a method of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase, comprising administering an effective amount of an agent, wherein the agent is an activator of endothelial nitric oxide synthase which antagonizes autoinhibition by a peptide region of endothelial nitric oxide synthase, wherein the region is between about amino acids 590-650 of endothelial nitric oxide synthase. Furthermore, it is requested that Group 4 be recombined with Group 32 and with Group 56, as Group 4 encompasses the agents of Claim 16 that are utilized in the methods of Group 32 and Group 56.

In addition, it is requested that Groups 39-44 (Claim 32) be recombined with elected Group 32, as these groups all pertain to methods of activating endothelial nitric oxide synthase, and because the activators used in the methods of Group 32 (i.e., the activator of Claim 16) and the methods of Groups 39-44 (i.e., the activators of Claim 19) share a commonality of function (activation of endothelial nitric oxide synthase).

It is also requested that Groups 62-67 be recombined with Groups 39-44 (and thereby with elected Group 32), because they similarly utilize the agents utilized in Groups 39-44; that is, they are drawn to methods of treating a disease modulated by production of nitric oxide by endothelial nitric oxide synthase, comprising administering an effective amount of an constitutive nitric oxide synthase activator peptide comprising an amino acid sequence selected

from the group consisting of SEQ ID NO:4-9 and activating fragments and derivatives of SEQ ID NO: 4-9 (Claim 19). Furthermore, it is requested that Groups 5-10 be recombined with Groups 39-44 and with Groups 62-67, as Groups 5-10 encompass the agents of Claim 19 that are utilized in the methods of Groups 39-44 and Groups 62-67.

Applicant also requests reconsideration of the restriction requirement in light of the exceptional burden it places upon the Applicant. The restriction essentially requires Applicant to file 83 or more applications to protect the subject matter which arose from the fundamental discovery described above. The expense from such a large number of filings, as well as the subsequent prosecution costs and maintenance fees associated with any issued patents, would be exceedingly high. Applicant requests that the Examiner reconsider the restriction and recombine the requested groups for these reasons as well.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call David E. Brook at (781) 861-6240.

Respectfully submitted,

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